Drug Profile Elobixibat for the Treatment of Constipation

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Abstract

Introduction: Chronic idiopathic constipation (CC) is highly prevalent worldwide. A subset of patients with CC have reduced fecal (and by inference, intra-colonic) bile acids (BA). Elobixibat, a locally-acting ileal bile acid transporter (IBAT) inhibitor, leads to increased BA delivery to the colon and represents a new class of treatment for CC. BAs accelerate colonic transit and increase colonic secretion. Therefore, IBAT inhibitors have potential to treat patients with CC.

Areas covered: *Rationale for IBAT inhibitor in therapeutics, and preclinical and clinical pharmacology of elobixibat:* In vitro, elobixibat is a highly potent, selective IBAT inhibitor. In humans, elobixibat accelerated colonic transit. In phase 2A, 2B and 3 studies in CC, elobixibat was efficacious, well tolerated and safe. An open-label, phase 3 trial (52 weeks) confirmed the safety of elobixibat. Elobixibat reduces LDL cholesterol, increases serum GLP-1, and has potential in metabolic syndrome.

Expert commentary: Uniquely among current treatments of CC, elobixibat stimulates both motor and secretory functions in the colon. These dual effects suggest that, when approved, elobixibat may be a first-line choice for constipation associated with colonic BA deficiency and a second-line treatment for all patients with CC and constipation-predominant irritable bowel syndrome. Further studies are required to confirm efficacy for relief of CC. Once approved, elobixibat will likely become a second-line choice for treatment of CC.

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1.0   Introduction

Increased fecal bile acids (BAs) and hepatic BA synthesis, which are markers of BA malabsorption or diarrhea, have been identified in patients with chronic diarrhea or diarrhea-predominant irritable bowel syndrome (IBS-D) [1,2]. In approximately 25-33% of patients with chronic functional diarrhea [3,4], excess BAs enter the colon and activate the various mechanisms listed in Table 1[5-29], resulting in diarrhea and abdominal discomfort. Shin et al. demonstrated that these biochemical changes translate to clinical findings. Participants with higher total fecal BAs had higher numbers of bowel movements, looser stool consistency, and faster colonic transit at 24 hours [1]. Other biomarkers in patients with IBS-D, in addition to elevated 48-hour total fecal BAs, are increased fasting serum 7-α-hydroxy-4-cholesten-3-one (7αC4) [2,30], decreased serum fibroblast growth factor 19 (FGF19) [31,32], and 75-selenium homocholic acid taurine (^{75}SeHCAT) retention <15% [3].

Conversely, there is now evidence that approximately 15% of patients with constipation predominant irritable bowel syndrome (IBS-C) has low 48-hour fecal BAs, and the proportion of lithocholic acid (LCA) (non-secretory BA) was increased and deoxycholic acid (DCA) (secretory BA) was decreased in IBS-C compared to controls [33]. Fasting serum 7αC4 was decreased (indicating decreased hepatic BA synthesis) and FGF19 was elevated (suggestive of increased negative feedback and, therefore, decreased hepatic BA synthesis) [33]. The associations of indices of BA synthesis or excretion with colonic functions were supported by 7αC4 being directly and FGF19 inversely correlated with colonic transit [33]. The reduction in total fecal bile acids and, particularly, decreased DCA in patients with functional constipation and IBS-C requires confirmation.

2.0   Body

2.1.   The enterohepatic circulation

BAs are detergent molecules that aid in fat and fat soluble vitamin absorption. BAs are synthesized within the liver from cholesterol via the addition of hydroxyl groups to the cholesterol ring, changing the structure and function of the sterol. They are subdivided into two categories: primary and secondary BAs [34]. Primary BAs are those synthesized and conjugated with glycine or taurine in the liver. The rate limiting step in hepatic BA synthesis is the addition of the hydroxyl group in the carbon-7 position via 7αC4. As noted in Figure 1, both primary BAs have an α-hydroxyl group in the carbon-7 position of the cholesterol ring [35]. Secondary BAs are the metabolites resulting from deconjugation and 7α-dehydroxylation of the primary conjugated BAs by colonic bacteria [36].

After synthesis and storage in the gall bladder, BAs are released into the duodenum after fat enters the small intestine and cholecystokinin is released, resulting in contraction of the gall bladder. BAs emulsify fat and allow absorption within the small bowel [37]. After fat moieties are absorbed, the intraluminal free BAs are reabsorbed within the terminal ileum via the IBAT, with an efficiency of approximately 95% [38]. As depicted in Figure 2 [39], having entered the ileal enterocytes, BAs then activate the nuclear farnesoid X receptor (FXR), which increases the transcription of FGF19 [5]. FGF19 acts as an endocrine

hormone, reaching the liver through the portal venous system. FGF19 binds to fibroblast growth factor receptor 4 (FGFR4) and klotho B, and this leads to inhibition of hepatic CYP7A1 (rate-limiting enzymes for synthesis of 7αC4 and the primary BAs) [38,40].

There are four major BAs in humans: chenodeoxycholic acid (CDCA), cholic acid (CA), deoxycholic acid (DCA), and lithocholic acid (LCA). As seen in Figure 1, these molecules differ structurally based on the locations of the hydroxyl groups, which alter the functions of the BAs [5,35]. CDCA (3α, 7α) and DCA (3α, 12α) have 2 α-hydroxyl groups which result in secretory properties compared to LCA which has non-secretory functions. In contrast, a fifth BA, ursodeoxycholic acid (3α, 7β), is a non-secretory BA in the colon [35].

3.0   Diagnostic testing for changes in bile acid synthesis or fecal bile acid excretion

There are presently two direct and two indirect methods of measuring excess or decreased BA synthesis or excretion. The two direct methods are the [75]Selenium HomotauroCholic Acid Test ([75]SeHCAT) retention and 48-hour total fecal BA excretion. The [75]SeHCAT utilizes radiolabeled BAs and monitors the percent retained over a period of seven days. Patients with excess BA loss have decreased retention (<15%) at seven days [3]. This test is available in Europe, but not in the United States. The alternative direct measurement of loss of BAs is the 48-hour total and individual fecal BA excretion; this requires ingestion of a 100-gram fat diet for four days with stool collection in the final two days [1,2,35]. Because of the dietary requirements and cumbersome stool collections required for measurement of fecal 48-hour bile excretion, patients may not be willing to complete this testing. Abnormal BA levels have been reported in patients with constipation; relative to healthy controls, there was reduced total fecal BAs and, specifically, DCA (which may result in reduced colonic secretion and motility) with increased LCA [33] and increased fasting plasma levels of taurine-conjugated DCA, CA, and LCA [41], which the authors attributed to greater BA reabsorption as a result of constipation.

The two indirect methods for measurement of BA balance are serum fasting biomarkers (7αC4 and FGF19) that indirectly measure BA synthesis. 7αC4 directly correlates with BA synthesis, and FGF19 indirectly assesses BA synthesis [30,31]. A meta-analysis evaluating the frequency of positive tests suggestive of BA mechanisms in functional diarrhea or IBS-D demonstrated yields of [75]SeHCAT of 0.308, total fecal BAs 0.255, 7αC4 0.171, and FGF19 0.248 [42]. However, it is important to note that none of the cohorts evaluated the diagnostic tests head-to-head.

4.0   Bile acids are physiological laxatives

Conjugated and non-conjugated BAs are physiologic laxatives that stimulate colonic motility [43] and secretion [44].

4.1.   Effects of bile acids on colonic secretion and motility

When BAs enter the colon, there are a number of mechanisms activated that result in increased colonic contractility, increased colonic mucosal permeability, increased water and

electrolyte secretion, and decreased water reabsorption. Table 1 summarizes the diverse mechanisms as summarized elsewhere [5].

BAs are known to stimulate colonic motility. Numerous studies have demonstrated increased colonic motility in both animals and humans after infusing DCA and CDCA, both of which are also secretory BAs (Table 1). BAs also activate TGR5 (takeda G-protein coupled receptor 5) receptors, induce high amplitude propagating contractions, and directly stimulate enteric neurons to increase serotonin secretion. All of these effects increase colonic motility.

4.2. Effects of bile acids on visceral sensitivity

Deoxycholic acid infusion into the colon resulted in persistent visceral hypersensitivity and referred pain in rats [45]. Another study evaluated esophageal pain with esophageal barostat balloon distension in 10 patients with functional heartburn and six healthy controls. There was a significant increase in pain when CDCA was infused via the nasogastric tube [46], indicating that the secretory BAs may play a role in visceral sensitivity.

4.3. Experimental effects of BAs on human colonic transit and bowel function

In a randomized, double-blind, placebo-controlled study of 20 healthy volunteers, delayed release formulation of sodium chenodeoxycholate (CDC) significantly accelerated colonic transit at 24 and 48 hours compared to placebo. It also significantly increased stool frequency, ease of passage and evacuation, and decreased stool consistency [47].

A randomized, controlled pharmacodynamics trial using the delayed release formulation of CDC in 36 females with IBS-C demonstrated a significant improvement in stool frequency, stool consistency and ease of passage compared to placebo [48]. In addition, CDC resulted in significant acceleration of overall colonic transit and ascending colon emptying (AC T½). There was a strong positive association between fasting serum 7αC4 and colonic transit (rs=0.749, p=0.003, placebo group) [48]. This trial further validated the role of BAs in the acceleration of colonic transit and the potential for exploring the role of modulating BA synthesis and enterohepatic circulation of BA pathways for the treatment of CC and IBS-C.

5.0 Proof of concept studies of IBAT inhibitor

5.1. Chemistry, preclinical pharmacology and pharmacokinetics of elobixibat

Elobixibat (formerly A3309) is an IBAT inhibitor that modulates the enterohepatic circulation of BAs. Elobixibat is a pure enantiomer of a synthetically modified 1,5-benzothiazepine, based on a seven-membered heterocyclic ring attached to a benzene ring (chemical formula $C_{36}H_{45}N_3O_7S_2$) [49] (Figure 3). The expected half-life ($T_{1/2}$) in humans is <4 hours. After oral administration, there is minimal systemic exposure, and systemically available drug is highly protein bound (>99.5%). After radiolabeling elobixibat and oral ingestion, there was limited tissue distribution and was found only in the gastrointestinal tract at 24 hours. The highest serum concentrations were found at 4 hours after individual dose or 2 hours after multiple doses over two weeks. There was no accumulation of elobixibat or associated metabolites within the plasma or urine.

Elobixibat does inhibit CYP3A4 *in vitro*. However, the significance of this inhibition in drug-drug interactions is limited, secondary to the decreased oral bioavailability.

Elobixibat is highly selective for IBAT, with an affinity more than 400-fold higher than for human liver sodium-dependent BA transporter and more than 1000-fold higher than for neutral amino-acid transporter [49].

5.1.1. In vitro studies in HEK293 cells—Elobixibat was found to be highly potent and selective for IBAT in an *in vitro* study in transfected HEK293 cells, which express various BA transporters (IC50=0.53±0.17 nM for the human transporter). In contrast, IC50 for binding to the human liver (basolateral) sodium/BA co-transporter was 0.24±0.02 μM. Thus, IBAT inhibition by elobixibat was 400-fold higher than the inhibition of the basolateral co-transporter and more than 1000-fold higher than the neutral amino acid transporters in HEK293 cells. Elobixibat is, therefore, highly potent and selective for IBAT in humans based on *in vitro* studies [49]. It is proposed that elobixibat acts as a partial inhibitor of the re-uptake of BAs in the terminal ileum, since there are still some BAs absorbed in a dose-dependent manner after elobixibat treatment, as illustrated by the incomplete suppression of FGF19 production or stimulation of 7αC4 levels [50].

5.1.2. In vivo preclinical model (constipated dogs)—When studied *in vivo* in dogs with constipation induced by a meat diet, elobixibat increased feces weight in a dose-dependent manner compared to the 5-HT$_4$ receptor agonist, tegaserod. This also correlated with a dose-dependent increase in serum 7αC4 concentration by 3- to 7-fold after 26 days of treatment. Given the duration of the biochemical effects, the data suggest that elobixibat has a lasting effect on increased BA synthesis in dogs with constipation, suggesting potential clinical utility [49].

5.2. Pharmacodynamics, safety and efficacy of elobixibat in humans

A summary of all the clinical trials discussed in the following section is available in Table 2 [50-54].

5.2.1. Phase 1b trial—In a phase 1b, randomized, double-blind, placebo-controlled trial conducted in 30 patients with chronic idiopathic constipation (CC), five escalating doses (range: 0.1, 0.3, 1, 3, and 10 mg/day) of elobixibat were studied in comparison to placebo over a 14-day period [50]. The study showed that, when administered orally, elobixibat was minimally absorbed and was present in picomolar concentrations in plasma. This supports the mechanism of action of elobixibat as a local inhibitor of IBAT [50]. Of note, the portion of absorbed elobixibat was mostly protein bound when in plasma, and the half-life was <4 hours. In the same cohort of patients with CC, elobixibat induced up to a 3-fold increase in BA synthesis as measured by serum 7αC4 and reduced the plasma FGF19 [50]. While the phase 1b trial was mainly focused on safety and tolerability of elobixibat, the efficacy of the drug was noted by changes in colonic transit time as measured by radiopaque markers. Compared to placebo, elobixibat, 10 mg, was effective in reducing colonic transit time, thereby demonstrating acceleration of colonic transit. Interestingly, elobixibat decreased plasma levels of total cholesterol and low-density lipoprotein (LDL) cholesterol in a dose-

dependent fashion [50], as increased BA synthesis in the hepatocytes, and directs sterols to the BA synthesis pathway and away from cholesterol synthesis. In this trial, elobixibat was found to be safe and tolerable across the dose levels tested with no serious adverse events or discontinuations. However, this phase 1b trial [50] of 14 days' duration did not represent evidence of efficacy for chronic constipation and, therefore, longer term studies were required, as discussed in the phase 2b (USA) trial [51] and the Japanese phase 3, open-label, 52-week trial [54].

5.2.2.   Phase 2a study—Elobixibat was studied in a phase 2a, double-blind, placebo-controlled, parallel-group study in 36 females with CC randomized to three groups (placebo, 15 mg or 20 mg elobixibat) for 14 consecutive days [51]. The primary endpoint for efficacy was colonic transit at 24 hours using scintigraphy [geometric center (GC) at 24 hours]. Secondary endpoints included other measurements of small bowel (colonic filling at 6 hours) and colonic transit (GC at 48 hours and ascending colon $T_{1/2}$), and symptoms-based (Bowel Pattern Diary) and biochemical [serum $7\alpha C4$, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, and LDL cholesterol] endpoints. Compared to placebo, elobixibat resulted in accelerated colonic transit, looser stool consistency, and reduced straining with defecation [51].

In general, elobixibat was well tolerated in this phase 2a trial, with only 1 of 13 patients in the placebo group and 2 of 12 patients in the 20 mg elobixibat group withdrawing from the trial due to diarrhea. There were no reported serious adverse events. The most common adverse event was mild/moderate abdominal cramps/pain that occurred in 36% of the 15 mg elobixibat group and 50% of the 20 mg elobixibat group (respectively, $p=0.039$ and $p=0.003$ compared to placebo). It was noted that abdominal cramps/pain tended to precede the diarrhea and were relieved by bowel movements [51].

5.2.3.   Phase 2b U.S. study—In a phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial conducted at 45 sites across the United States, 190 patients with CC (90% female) were randomized into four groups (placebo, 5, 10, or 15 mg/day elobixibat) over 8 weeks [52]. In this trial, the primary endpoint was change in the number of spontaneous bowel movements (SBMs) during week 1 compared to baseline. The secondary endpoints were similar to the phase 2a trial [weekly evaluation of SBMs and complete spontaneous bowel movements (CSBMs), daily stool consistency and straining, abdominal discomfort, serum $7\alpha C4$, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides] except for the absence of measurements of colonic transit [52].

Elobixibat resulted in a significantly greater increase in the number of SBMs during week 1 from baseline compared to placebo [mean increase (95% confidence interval): 1.7 (0.7, 2.8) for placebo, 2.5 (1.5, 3.5), 4.0 (2.9, 5.0), and 5.4 (4.4, 6.4) for 5 mg, 10 mg ($p<0.002$), and 15 mg ($p<0.001$) elobixibat, respectively]. Elobixibat also resulted in increased stool frequency that was maintained over the 8-week treatment period. Additionally, patients in the elobixibat treatment arms reported decreased straining and bloating compared to the placebo group ($p<0.05$) [52].

Similar to previous trials, individuals with CC treated with elobixibat had increased 7αC4 and reduced LDL cholesterol. Similar to the phase 2a trial, elobixibat was well tolerated, with the most common adverse events being abdominal pain and diarrhea (more commonly in the 15 mg group). A total of 29 patients discontinued the trial (n=6 in each of placebo, 5mg and 10mg elobixibat groups; n=11 in the 15 mg elobixibat group). The majority of the discontinuations in the elobixibat treatment groups were related to adverse events, whereas, in the placebo group, the main reason for discontinuation was due to lack of efficacy [52].

5.2.4. Phase 2b Japan trial—In order to determine the optimal dosing of elobixibat for treatment of CC in Japanese patients, Nakajima et al. conducted a randomized, placebo-controlled trial in 163 patients randomized to four groups (placebo, 5, 10 or 15 mg/day elobixibat, orally) for 2 weeks [53]. The primary endpoint was the change from baseline in frequency of SBMs at end of the first week of treatment. Individuals treated with 10 mg or 15 mg elobixibat had a significant change from baseline in the frequency of SBMs [mean ± standard deviation, 5.7±4.2 (p=0.0005) and 5.6±3.5 (p=0.0001) times per week, respectively] compared to the placebo group (2.6±2.9 times per week). In addition, a subgroup analysis demonstrated elobixibat to be equally efficacious in patients with CC with or without IBS. The authors concluded that 10 mg elobixibat is the clinically optimal dose for treatment of CC in a Japanese cohort [53].

Similar to the previous trials, elobixibat was well tolerated, with the most common adverse events being mild abdominal pain and diarrhea in the treatment groups, and with no serious adverse events. Only 9/163 patients in the elobixibat groups discontinued the trial due to adverse events, and 1/40 in the placebo group discontinued due to lack of efficacy [53].

5.2.5. Short-term safety and efficacy, long-term safety and quality of life in Japanese phase 3 trials—Nakajima et al. conducted two phase 3 trials in patients with CC to determine the safety and efficacy of short-term treatment with elobixibat (Trial 1), and the safety, satisfaction and quality of life (QOL) with long-term treatment with elobixibat (Trial 2) [54].

5.2.5.1. Trial 1 (short-term treatment): Trial 1 was a randomized, double-blind, placebo-controlled study in 133 patients with CC conducted at 16 clinics in Japan comparing 10 mg/day elobixibat to placebo for two weeks. The primary outcome was change from baseline during week 1 in the frequency of SBMs. During week 1, the change in SBM frequency/week was significantly increased in the elobixibat group [n=69, 6.4 (5.3, 7.6), least squares mean (95% CIs)] compared with placebo [n=63, 1.7 (1.3, 2.2), p<0.0001]. Elobixibat was well tolerated in this two-week trial, with only 4/133 patients withdrawing due to adverse events [abdominal pain (18.8%) and diarrhea (13.0%)] [54].

5.2.5.2. Trial 2 (long-term, open-label treatment): Trial 2 was an open-label study in 340 patients with CC conducted at 34 clinics or hospitals in Japan over a period of one year. Participants were allowed to titrate the dose of elobixibat (5-15 mg/day) after 1 week of 10mg/day, based on the effectiveness of the drug and adverse events. The primary outcome of Trial 2 was to assess the safety of long-term use of elobixibat. Secondary outcomes

focused on evaluation of efficacy relative to baseline, including bowel function assessment and health-related quality of life (QOL) and satisfaction scores.

Elobixibat was found to be safe, with no reported serious adverse events or deaths over the one-year period. Similarly, the most common adverse events in the elobixibat treatment group were abdominal pain (24.1%) and diarrhea (14.7%). Only 18/340 patients discontinued treatment due to adverse events. Approximately 25% of patients titrated the dose up to 15 mg/day and 25% of patients titrated the dose down to 5 mg/day within one month after their initial dose. Ultimately, there was approximately 33% of patients in each dose group of 5 mg, 10 mg or 15 mg [54].

Additionally, patients reported consistent improvements from baseline in numbers of SBMs and CSBMs, stool consistency, and QOL. The effects of elobixibat were sustained throughout the one-year treatment period.

6.0 Metabolic effects of elobixibat

Previous clinical trials of elobixibat in patients with constipation thus far have analyzed its effects on total cholesterol, LDL and HDL cholesterol as a secondary biochemical endpoint [50-54]. Interestingly, in all these trials, except for the short duration pharmacodynamics study of Wong et al. (phase 2a trial) [51], there was a significant reduction in total cholesterol and LDL cholesterol in a dose-dependent manner, with no effect on HDL cholesterol. This is consistent with results showing reduced ileal BA absorption in the ileum, reduced FXR stimulation and production of FGF19 leading to reduced negative feedback of hepatocyte BA synthesis, and, therefore, shunting of steroid synthesis in the hepatocyte from cholesterol and LDL cholesterol to increased BA synthesis [50-54].

A more specific assessment of the effects of elobixibat on lipid metabolism was conducted in a single-center, randomized, parallel-group, double-blind, placebo-controlled trial in 36 dyslipidemic patients treated for 28 consecutive days. In this trial, the primary endpoint was reduction in LDL cholesterol. At a dose of 5 mg, elobixibat reduced LDL cholesterol by 7.4% and decreased the LDL/HDL ratio by 18% [55]. The effect on LDL cholesterol alone with reduction in the LDL/HDL ratio is of particular importance for prevention of cardiovascular disease (CVD) [56]. Additionally, it is worth noting that constipation is reported to be a risk factor for CVD disease, as demonstrated in a study of post-menopausal women with severe constipation who had an approximate 25% increased risk of CVD attributable to the constipation [57]. Furthermore, patients with CVD had decreased fecal BA excretion in comparison to those without CVD [58]. These observations suggest that elobixibat may be potentially beneficial in women with constipation who also have risk factors for CVD [55].

Finally, elobixibat plays a role in stimulating the synthesis and secretion of glucagon-like peptide-1 (GLP-1), presumably due to the increase in colonic BAs, which would stimulate the TGR5 receptors on the intestinal L cells, that is, enteroendocrine cells that synthesize and secrete GLP-1 [55]. Additionally, the release of GLP-1 in response to IBAT inhibition

by elobixibat can provide an explanation for the observation of delayed gastric emptying in contrast to the acceleration of colonic transit in response to elobixibat [51].

7.0   Conclusion

Elobixibat is a novel pharmacologic treatment for chronic constipation with promising results. Elobixibat was approved on January 19, 2018 by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) on the basis of these results.

8.0   Expert commentary

Chronic constipation is a highly prevalent condition worldwide, affecting approximately 27.2% of people in North America [59] and 28.4% of Japanese adults [60]. To date, pharmacologic advancements for treating CC have targeted increasing colonic motility via 5-HT$_4$ receptor agonists and increasing colonic secretion with both osmotic laxatives and intestinal secretagogues [e.g. lubiprostone (activation of chloride channels) and linaclotide and plecanatide (guanylate cyclase C agonists)] [61]. Elobixibat provides a novel mechanism of action targeting the IBAT and increasing colonic bile acid, which active both increased colonic motility and secretion via the mechanisms listed above [44,50,51].

The multiple clinical trials evaluating elobixibat have demonstrated a consistent improvement in stool frequency and consistency, clinically meaningful endpoints, across various populations diagnosed with CC. Moving forward, it will be interesting to evaluate elobixibat's efficacy in patients with IBS-C. The main concern is that abdominal pain may increase in this patient population. However, improvement of the constipation may improve the baseline abdominal pain that is associated with long-standing constipation. Additionally, further evaluation is needed to determine elobixibat efficacy in patients with normal versus low total fecal bile acids. In a hypothesis generating paper, 15% of patients with IBS-C were found to have reduced total fecal BAs, which correlated with physiological endpoints of retarded colonic transit [33]. The current trials of elobixibat in CC did not select participants with low BA synthesis. Despite that, elobixibat was efficacious in the treatment of CC. Prior to U.S. Food and Drug Administration approval, further investigation is required with 12-week, phase 3, randomized, controlled trials to confirm the efficacy for relief of CC and IBS-C. Once approved, we anticipate that elobixibat will become a second-line therapy for patients with CC. Although the cost of this medication will need to be considered to appraise its cost-benefit ratio, it is worth noting that emergency room visits for constipation are steadily rising with an associated cost of $1.6 million in 2011 [62]. After elobixibat is approved, it will be necessary to conduct studies to determine whether the efficacy leads to saving on health care dollars in both emergency room visits and hospitalizations associated with CC.

There are no genetic variations that would suggest clinically significant ethnic or racial differences in response to elobixibat among these populations. Indeed, the phase 2a and 2b studies conducted in the U.S., the phase 1 study conducted in Scandinavia, and the phase 2b and phase 3 studies conducted in Japan provide very similar results. This is more clearly apparent in Table 2 (49-53).

The previous clinical trials have not evaluated the pharmacogenetics of elobixibat in association with allelic variants in IBAT and other BA receptors. Rao et al. studied the role of genetic variations in proteins involved in the FGF19-mediated feedback control of BA synthesis in response to CDC, which had an influence on ascending colon emptying [48]. Thus, future trials should also focus on the effects of such genetic variations (e.g., FGFR4 or klotho ß) and the response to elobixibat. This would allow for individualizing therapy in those variants with a better response.

Interestingly, there was a similar rise in GLP-1 with both elobixibat and dipeptidyl peptidase IV inhibitors (DPP4 inhibitors) such as vildagliptin [55,63]. Based on a meta-analysis of DPP4 inhibitors, there was an overall decrease in HbA1c of 0.77% (95% CI 0.72 - 0.82%), and future studies will need to assess whether elobixibat enhances glycemic control [64]. The positive effect of elobixibat on GLP-1 secretion may benefit patients with type 2 diabetes mellitus or pre-diabetes, but this would require additional clinical trials.

In conclusion, although it is still early to generalize, we anticipate that, once elobixibat is approved, it will be widely available for the treatment of CC and IBS-C. More data are still required prior to making elobixibat available for prescribers, such as a phase 3 trial for CC over 12 months. In the coming years, elobixibat is likely going to be approved and available in the U.S. since it is, ultimately, a promising novel drug with a favorable profile for the treatment of CC and IBS-C. Alternative indications might be possible in the next five years, given the potential benefits in treating metabolic diseases such as hyperlipidemia and type 2 diabetes mellitus. It is conceivable that the metabolic effects of elobixibat, probably mediated by effects of BAs on enteroendocrine cells, will have potential benefits in patients with CC and type 2 diabetes.

Acknowledgements

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Papers of special note have been highlighted as:

* of interest

** of considerable interest

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Key Issues

- The enterohepatic circulation is an efficient method of recycling bile acids (BAs) and involves several key molecules: the ileal bile acid transporter (IBAT), farnesoid X receptor, the hormone fibroblast growth factor 19 (FGF19), and 7-α-hydroxy-4-cholesten-3-one (7αC4), the intermediary step in conversion of cholesterol to BAs. Free BAs are efficiently reabsorbed (~95%) in the terminal ileum via the IBAT.

- Conjugated and non-conjugated BAs are physiologic laxatives that stimulate colonic motility and secretion.

- Elobixibat is a highly potent and selective IBAT partial inhibitor that modulates the enterohepatic circulation of BAs, resulting in increased BAs in the colon and compensatory increase in hepatic BA synthesis from cholesterol.

- The use of elobixibat in individuals with chronic constipation (CC) results in faster colonic transit, increased spontaneous bowel movements (SBMs) and complete SBMs. Elobixibat was found to be safe and well tolerated across the dose levels tested in phase 2B and 3 trials, with no serious adverse events or discontinuations.

- Metabolic effects of elobixibat include reduction of serum LDL cholesterol, reflecting diversion of sterols to BA synthesis.

- Elobixibat increases circulating levels of glucagon like peptide-1 (GLP-1), presumably reflecting BA stimulation of enteroendocrine cells.
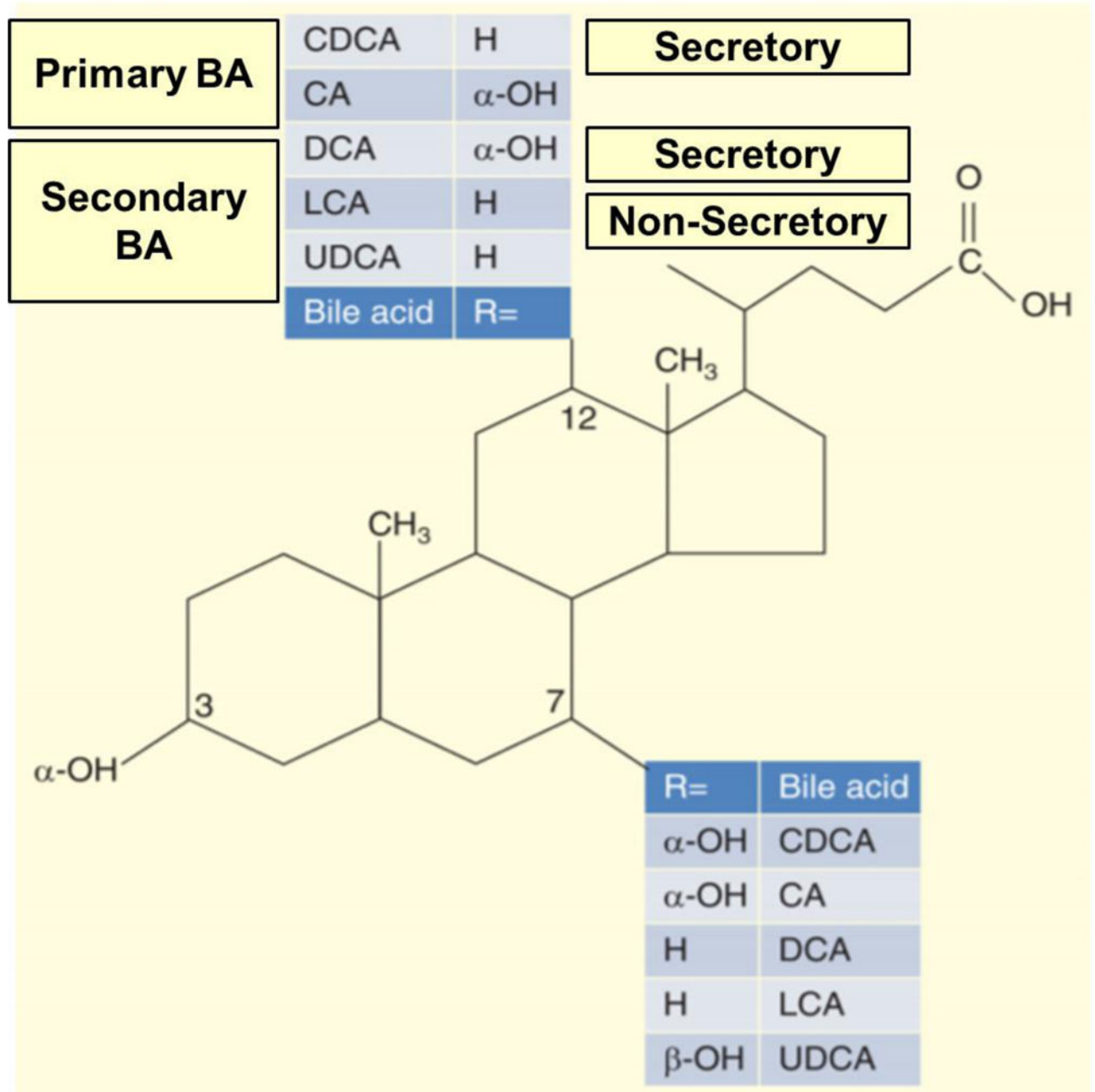
Primary BA	CDCA	H	Secretory
	CA	α-OH	
Secondary BA	DCA	α-OH	Secretory
	LCA	H	Non-Secretory
	UDCA	H	
	Bile acid	R=	

R=	Bile acid
α-OH	CDCA
α-OH	CA
H	DCA
H	LCA
β-OH	UDCA

Figure 1. Chemical structures and colonic functions of individual bile acids. Modified with permission from reference 35.

BA, bile acids; CDCA, chenodeoxycholic acid; CA, cholic acid; DCA, deoxycholic acid;

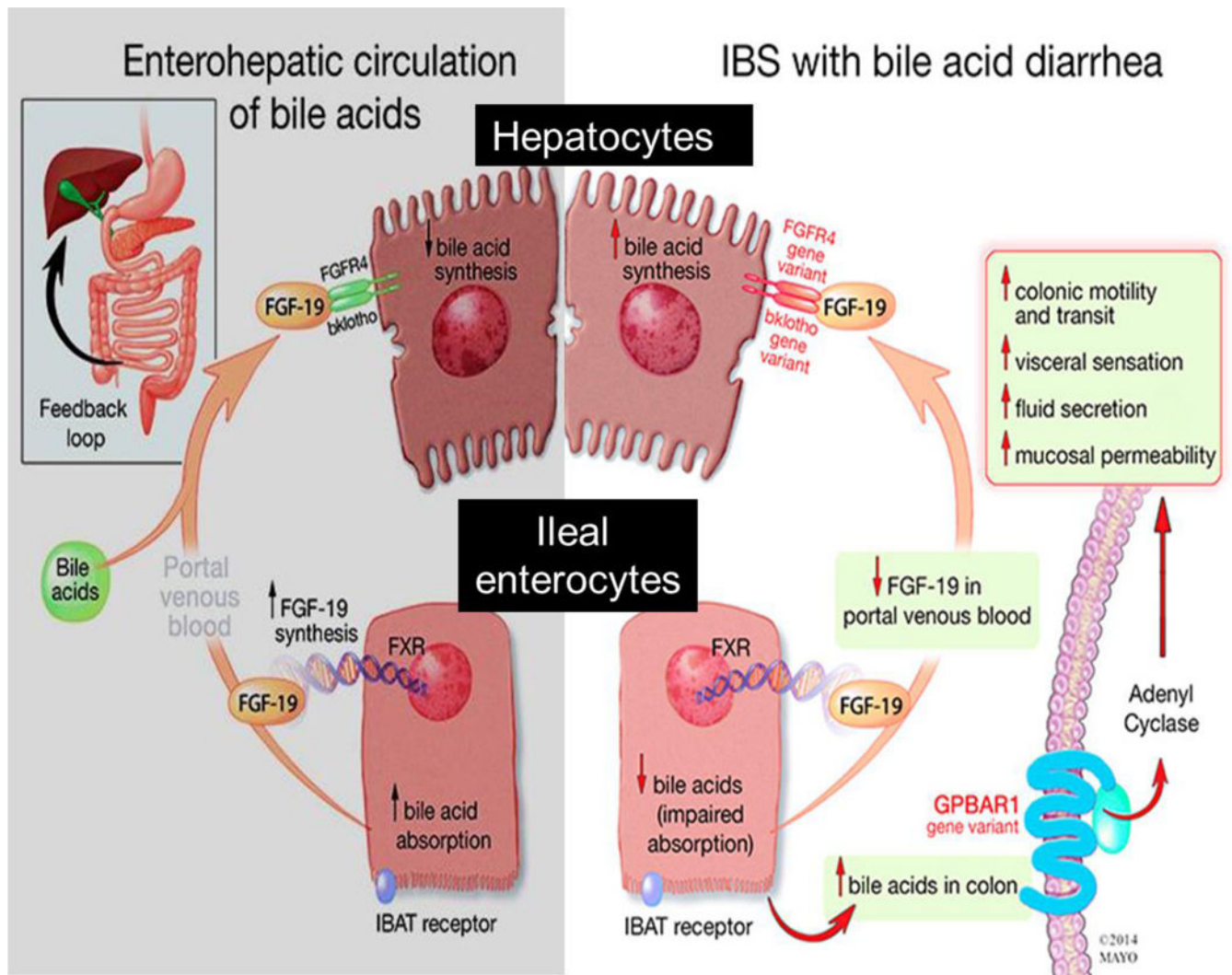LCA, lithocholic acid; UDCA, ursodeoxycholic acid

Figure 2.
Enterohepatic circulation. The left panel shows the enterohepatic circulation in patients
without bile acid malabsorption. The right panel demonstrates enterohepatic circulation in
patients with bile acid malabsorption. Reproduced from reference [39] (no permission
needed; it is a free PMC article). IBAT, ileal bile acid transporter; IBS, irritable bowel
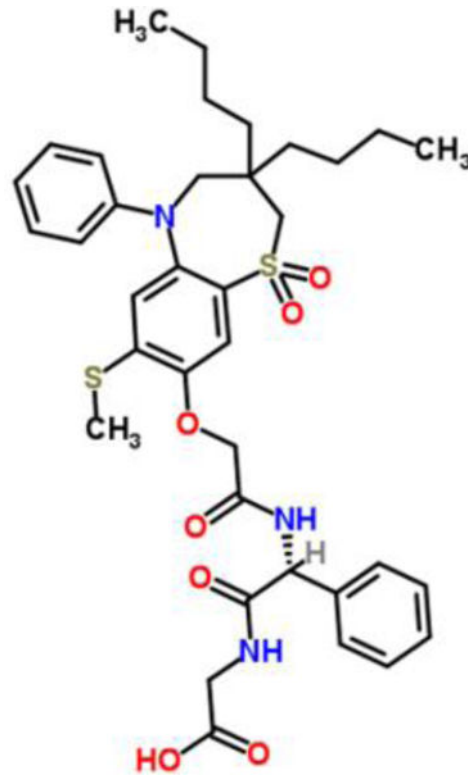syndrome;

Figure 3.
Two dimensional molecular structure of elobixibat

Table 1.

Mechanisms of stimulation of colonic water and electrolyte movements and motility by BAs. Adapted with permission from reference 5.

Mechanism	Mediators/Co-factors	Effects
Stimulation of intracellular mediators [6-11]	↑cAMP, epidermal growth factor receptor, and mediators including exchange protein directly activated by cAMP and Ca^{++} ions	CFTR - induced chloride secretion
↑ intestinal permeability [12-15]	detergent or structure-activity properties of the BAs, TGR5 activation, ↓occludins	↑ secretion, ↑ motility, ↓ transepithelial barrier
Aquaporin channels [16,17]	↑ aquaporin channels 3 and 8 in rats	↑ water secretion
Enteroendocrine mechanisms [18-21]	↑ serotonin	↑ fluid and mucus secretion; activation of enteric neurons to ↑ colonic motility
Neurocrine mediation [21-25]	Activate basal TGR5 and submucosal cholinergic neurons; TGR5 activation of cholinergic and nitrergic myenteric neurons	↑ colonic motility, transit and secretion
Decreased sodium and water absorption [26]	↓ sodium potassium ATPase β1 unit in colon and α1 unit in proximal colon	↓ sodium and water reabsorption
↑ Myoelectrical activity [27-29]	Mechanism(s) unclear	↑ motility index
↑ HAPC [23]	↑ frequency of colonic propagating pressure wave sequences; mechanism(s) unclear	↑ colonic mass movements

ATP, adenosine triphosphatase; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator

Table 2.

Summary of the clinical trials in chronic constipation

[<3 spontaneous bowel movements (SBM)/week + lumpy and or hard stools, straining and sensation of incomplete evacuation during defecation; pain not a predominant symptom]

Author, year	Dose (mg/day)	Simren et al. 2011 [50]	Wong et al. 2011 [51]	Chey et al. 2011 [52]	Nakajima et al. 2018 [53]	Nakajima et al. 2018 - 2wk RCT [54]	Nakajima et al. 2018 - 52wk open label [54]
N (F/M)		30 (23/7)	36 (36/0)	190 (170/20)	163 (143/20)	132 (109/23)	340 (283/57)
Study duration, wk		2	2	8	2	2	52
Location of Study		**Sweden**	**USA**		**Japan**		
Primary Outcome		Safety	Colon transit	SBM	SBM at wk1	SBM at wk1	Safety, SBM and satisfaction over 52 wks
BSFS (1-7 scale)	3	↑					
	5			↑ 1	↑ 1.3		
	10	↑		↑ 1	↑ 1.7	↑ 1.8	
	15		↑ 1.3	↑ 1	↑ 2.0		
	20		↑ 1.8				
Stool (SBM) #/ day	3	↑					
	5			↑ 2.5	↑ 1.7		↑ 3.3[*]
	10	↑		↑ 4.0	↑ 4.1	↑ 6.4	↑ 3.3[*]
	15		↑ 0.5	↑ 5.4	↑ 3.8		↑ 3.3[*]
	20		↑ 1.17				
AE: Abdo pain	3						
	5			10%	23%		24%[*]
	10			11%	26%	19%	24%[*]
	15		36%	27%	12%		24%[*]
	20		50%				
AE: Diarrhea	3						
	5			8%	9%		15%[*]
	10			6%	5%	13%	15%[*]
	15		9%	13%	7%		15%[*]
	20		36%				

[*] Refers to the average response over 5 mg, 10 mg, and 15 mg. There were equal proportions of patients with each dose listed.